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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,108	12/20/2001	Timothy David Osslund	01017/38834F	7916

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,108	OSSLUND, TIMOTHY DAVID	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/6/05.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 62-83 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 62-83 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

DETAILED ACTION

1. Applicant is advised that the Notice of Allowance mailed is vacated. If the issue fee has already been paid, applicant may request a refund or request that the fee be credited to a deposit account. However, applicant may wait until the application is either found allowable or held abandoned. If allowed, upon receipt of a new Notice of Allowance, applicant may request that the previously submitted issue fee be applied. If abandoned, applicant may request refund or credit to a specified Deposit Account.

2. Prosecution on the merits of this application is reopened on claims 62-83 considered unpatentable for the reasons indicated below:

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66-83 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not support the combination of elements currently claimed i.e. Lys to Arg substitutions at positions 17, 35 and 41, in combination

with another substitution. Claims 66-83, require the Lys to Arg substitutions at positions 17, 35 and 41, in combination with introduction of a Lys in an "internal core helix". There is no support for changing an internal core helix of G-CSF. In contrast the specification discloses that generally, for the G-CSF internal core, the internal four-helix bundle lacking the external loops, the hydrophobic internal residues are essential for structure integrity (page 66). Because the claims require that there be a change to the internal core helix which is not essential for structural integrity, there is clearly no written description in the specification for that limitation. The specification lists one possible variant molecule Lys to Arg substations at positions 17, 35 and 41. There is no demonstration that applicants were in possession of a G-CSF variant with those specific Lys to Arg substation, in combination with introduction of a Lys in an "internal core helix" of G-CSF. Applicant was not in possession of such a G-CSF variant because the specification teaches that residues in the "internal core" are necessary to maintain structure, and nowhere suggests modification of any of those residues. Also there is no suggestion of making lysine alterations in the internal core helices and to PEGylate such lysine residues. There is no suggestion to combine the PEG modification with changes of the Lys to Arg mutations at positions 16, 34 and 40. The only suggestion in the specification is for making lysine alterations for the loop regions of the G-CSF molecule and not in the helices. There is no enablement for the change in internal core helix because the specification does not suggest modifying these residues, but teaches that mutations should be made in other regions of the G-CSF molecule (the loops)

and that mutations should not be made in the helical regions. The claim contains new matter and for the reason given above is rejected.

3. Claims 62-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a G-CSF variant wherein the lysines residues 17, 35, and 41 contained in the polypeptide of SEQ ID NO:2 are substituted with arginine , does not reasonably provide enablement for G-CSF variants having any amount of hematopoietic activity and having any number of alterations in the internal or external loops. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention.

The claims read on any G-CSF variant having the indicated functional activity and having any number of alterations to the protein so long as it comprises at least 3 arginine residues at positions 17, 35, and 41 of the

polypeptide disclosed in SEQ ID NO:2 and an unlimited number of lysines containing PEG. The claims provide no minimal limit on the level of hematopoietic activity that the G-CSF variant must have. In support of the claims, the Applicant has provided a single working example (Lys to Arg substations at positions 17, 35 and 41) variant disclosed in the Table 2 of the specification. The application also purports to provide guidance as to which amino acids within the external or internal loops may be altered so as result in an active G-CSF variant. However, given the scope of the claims, the single working example and the provided guidance are not found sufficient to enable the making and use of G-CSF variants to the full extent as claimed. With reference to the single working example provided, it is noted that the literature indicates that the art of protein modification is highly unpredictable. See e.g., Bowie et a1., Science 247: 1306-10 This reference teaches that, although proteins are generally amenable to alteration, the effect of any particular alteration on the structure and activity of a protein is not predictable without teachings as to the relationship between the altered residues and the protein's structure and function. Also the unpredictability is highlighted by applicant's specification which discloses that generally, for the G-CSF internal core, the internal four-helix bundle lacking the external loops, the hydrophobic internal residues are essential for structure integrity (page 66). Claims 66-83 require the mutation of the internal core helices. These mutations will produce inactive variants. The specification teaches away from what the claims are claiming as useful. In view of this

unpredictability, the presence of a single working example is insufficient to demonstrate the enablement of the entirety of the claimed genus.

As indicated above, the claims place no limit on either the number of residues that may be modified, or present a minimal level of hematopoietic activity required. For the reasons indicated above, the lack of predictability about the effects of any particular modification or combination thereof those in the art have also not been enabled for the making and use of any number of modifications that maintain the G-CSF activity. The mere presence of hematopoietic activity, no matter how low, would not necessarily enable those in the art to use the G-CSF variants. Further, the teachings of the application do not permit those in the art to readily predict which residues of combination of residues would result in such low but nonetheless usable levels of activity. For these reasons, the application is not found enabling for the making and use of G-CSF variants as claimed. The application has not provided sufficient information to enable the practice of the claimed invention with any G-CSF variant with any level of in hematopoietic activity less. The claims are therefore rejected as exceeding the scope of inventions for which the application has provided an enabling disclosure.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 62-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Shaw (US Patent 4,904,584).

Shaw (US Patent 4,904,584) discloses the "site-specific homogenous modifications of polypeptides" as well as substitutions of lysine residues 16, 23 and 34 with arginine (see, e.g., cols. 9-10, Table2, listing modification of lysine residues at positions 16, 23, 14 and 40). The lysine residues 16, 23, 34 and 40 disclosed by Shaw correspond to lysine residues 17, 24, 35 and 41 of instant application. SEQ ID NO:2 of instant application contains the optional N-terminal methionine residue at position 1, in contrast Shaw teaches the G-CSF molecule disclosed in Figure 4, which does not contain the optional N-terminal methionine. As such, the numbering used by Shaw is one amino acid lower that that used in instant specification. Shaw also teaches the modification of proteins by replacing naturally occurring lysine residues with non-lysines, preferably arginine, and substituting a lysine for a non-lysine residue. Abstract, col. 3, lines 36-43. The reference teaches that such modification is performed so as to control the attachment site of a molecule, such as PEG, to the protein, Col. 1. Shaw further teaches that in addition to modification of G-CSF by substituting the lysine

residues with arginine, and other lysine residue can be used for PEG attachment. Therefore since Shaw teaches the same mutations disclosed in claims 62-65 it meets the limitations of said claims, absent evidence to the contrary.

Claim Rejection, 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 62-83 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 62 and 66 and are indefinite because it is not clear what is meant by the phrase "at least one external loop is altered to include one or more lysines containing at least one PEG" . PEG molecules can be attached to lysine residues but it is not clear how a lysine residue would "contain" a PEG.

Claim 75 is indefinite because it is not clear what is meant by the phrase "at least one internal core α-helix amino acid sequence is altered to include one or more lysine residues containing at least one PEG". PEG molecules can be attached to lysine residues but it is not clear how a lysine residue would "contain" a PEG.

Claim 76 is indefinite because it is not clear what is meant by the phrase "at least two internal core α-helix amino acid sequence is altered to include one

or more lysine residues containing at least one PEG". PEG molecules can be attached to lysine residues but it is not clear how a lysine residue would "contain" a PEG. Further the phrase "at least two internal core α-helix amino acid sequence is altered" is confusing. It appears applicant is claiming the attachment of PEG to one or more lysine residues contained in at least two internal core α-helices. Alternative language should be used to distinctly claim the subject matter which applicant regards as the invention.

Claim 79 is indefinite because it is not clear what is meant by the phrase, "at least three internal core α-helix amino acid sequence is altered to include one or more lysine residues containing at least one PEG". PEG molecules can be attached to lysine residues but it is not clear how a lysine residue would "contain" a PEG. . It appears applicant is claiming the attachment of PEG to one or more lysine residues contained in at least three internal α-helices. Alternative language should be used to distinctly claim the subject matter which applicant regards as the invention.

Claims 63-65, 67-74, 77-78, 80-83 are indefinite for depending on an indefinite base claim and fail to resolve the issues raised above.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on 571272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
July 1, 2005

JOSEPH MURPHY
PATENT EXAMINER